The following remarks are supplemental to amendments and responses filed on November 8, 1995; January 3, 1996; and February 7, 1996. Claims 5-6 are withdrawn from consideration. Claims 1-4 and 7-9 were variously rejected under 35 USC §§ 102, 103, and 112. Claims 2-3 were canceled and new claims 10-26 were added in the amendment of February 7, and fall within the elected group. The amendment of November 8 was responsive to all grounds of rejection. Supplemental amendments and arguments pertaining to the § 112 rejections were provided in the response of February 7. This paper provides supplemental arguments pertaining to the prior art rejections made under 37 USC §§ 102 and 103. The remarks and amendments made previously and herein are believed to place the application in condition for allowance, which is respectfully requested.

REMARKS

35 USC § 102 rejection over Bhattacharya-Chatterjee et al.

Claims 1-3 were rejected under § 102(b) over a 1993 publication by Bhattacharya-Chatterjee et al. 1993. Claim 1 has been amended, and claims 2 and 3 have been canceled. Claim 1 and new claim 11 pertain to an antibody having the identifying characteristics of the 1A7 antibody or an antibody produced by the cell deposited under ATCC Accession No. HB-11786. New claim 10 pertains to the deposited cell line, and new claim 12 pertains to antibody purified from the cell line. Applicants respectfully traverse the § 102 rejection over Bhattacharya-Chatterjee et al., rejection, and ask that it be reconsidered and withdrawn.

The cited reference is a one-paragraph abstract that discloses the existence of the preliminary 1A7 antibody-producing cell line, and describes the immunizing antigen used (14G2a) along with some of the characteristics of 1A7. No sequence data is provided, and no statement is included as to the availability of the antibody or the cell line.

As stated in the response of November 8, 1995, it is applicants' position that this reference is not enabling for the claimed invention. This is further elucidated by the following.

First, the claims at issue relate to the 1A7 antibody *itself*. In the Office Action, the Examiner required a deposit of the 1A7 producing cell line to satisfy the enablement requirements of 35 USC § 112 ¶ 1. By this requirement, the Examiner has admitted that the cited abstract is not enabling for the claimed invention.

In addition, the following sections provide further support for applicants' position. The main points of the argument are:

1. The legal standard for a 35 USC § 102 reference is that it must enable the public to make and use the substance that is claimed. A method for making a general category of substances does not enable a single species where the probability of reproducing the species by the method is so remote as to be unworthy of serious consideration.
2. The process whereby antibody sequences are generated means that mature antibodies have unique and unusual sequences.
3. The 1A7 antibody is a mature antibody with unique and unusual sequences. The probability of reproducing 1A7 by immunizing a second animal is so remote as to be unworthy of serious consideration.
4. The 1A7 antibody, the antibody-producing cell, and the sequence data have not been available to the public. Accordingly, the invention cannot be said to be in the possession of the public.
5. Since the legal standard requires a § 102 reference to place the claimed invention into the possession of the public, the cited abstract does not meet the legal standard. Accordingly, the claimed invention is patentable over the cited abstract.

1. The legal standard for enablement of a 35 USC § 102(b) reference

It is well established that a reference must be enabling if it is to constitute a statutory bar to patentability under 35 USC § 102(b). Even if a general description has previously been made by the same inventor, a particular species not in possession of the public may nonetheless be claimed and patented.

The Examiner's attention is directed in particular to *In re LeGrice* (133 USPQ 365 (CCPA 1962)), which has some instructive parallels with the present case. Copies of the decision is enclosed for the Examiner's convenience.

In re LeGrice concerned two breeds of roses which the PTO Board of Appeals had held to be unpatentable. The Board had rejected the application for a plant patent under 35 USC § 102(b), citing a prior description and pictoral representation of the same breeds in a publicly available catalog.

The CCPA established that plant patent applications were to be treated no differently than utility patents under 35 USC § 102(b). With respect to the enablement requirement of § 102(b), it stated:

> We think it is sound law, consistent with the public policy underlying our patent law, that before any publication can amount to a statutory bar to the grant of a patent, its disclosure must be such that a skilled artisan could take its teachings in combination with his own knowledge of the particular art and be in possession of the invention.
>
> – *In re LeGrice* at 372.

The court held that enablement of a prior art reference was to be evaluated on a case-by-case basis. It dealt with the situation at hand as follows:

> Commercial rose-breeders, particularly in this country and England, continually strive to develop new varieties with characteristics of interest to commercial and amateur rose growers. A few of these characteristics are color, fragrance, freedom from various diseases, abundant foliage, firmness, size and shape of flower, number and frequency of blooms, etc. Each of these characteristics is a sex-linked characteristic and as such is subject to the applicable principles of plant heredity and the transmission of inheritable characteristics. ...
>
> The rosa floribunda plants described in the two applications on appeal and in the publications were produced by sexual propagation as a result of the chance rearrangement of the almost infinite number of variables arising from the particular chromosomes of the parent plants. ... The parentage of the "Charming Maid" rose is given in the Rose Annual of 1954 as "Dainty Maiden x Mrs. Sam McGredy." To those skilled in the art of rose breeding this indicates that the parent "Dainty Maiden" is the seed parent, i.e., that this parent was selected by the breeder to bear and develop seeds which result from pollination of its emasculated flowers with pollen taken from the other parent, "Mrs. Sam McGredy."
>
> The production of seeds by cross-pollination does not assure the plant breeder that he has produced a true new plant variety having the characteristics desired. At this step, the principles of heredity and plant genetics introduce such variables that no two seeds from the parent cross can be expected to produce identical plants.
>
> – *Id.* at 372; footnotes omitted

The court recognized that between the reference and knowledge in the art, the public was in possession of: a) the genetic heritage of the new variety, as inherent in the parentage; b) the process whereby parent roses are crossed to obtain a new variety; c) certain desirable characteristics of the new variety listed in the catalog description, including size, color, fragrance, growing characteristics, and general effect; and d) as many desirable characteristics of the new variety as may be discerned from the color reproduction.

Nevertheless, the court rejected the view that this enabled a practitioner in the art to obtain the variety sought to be patented. The process of cross-breeding involves genetic recombination between the parent strains. Even though a practitioner might successfully obtain a cross with similar appearance and characteristics based on the catalog description, the cross

would not have the same genetic composition. This in turn could affect some of the more subtle features of the rose.

In effect, the court asserted that a description of how to make a general category of substances (i.e., all the possible cross-breads) does not enable a single species (the Charming Maid rose), where: a) the relevant claims are restricted to the species; and b) the probability of reproducing the species by the disclosed method is highly improbable.

The improbability of obtaining or even predicting the claimed invention has been at the center of a number of recent decisions. In *In re Bell* (26 USPQ2d 1529 (Fed. Cir. 1993)), the naturally occurring encoding sequence of human insulin-like growth factor (IGF) was held to be patentable even though the amino acid sequence was previously known. The amino acid sequence rendered predictable 10^{36} different nucleic acids that might potentially code for IGF. However, the prior art did not suggest which of these 10^{36} possibilities was the naturally occurring gene sequence, and the relevant claims were to this one sequence. Accordingly, the claimed invention would not have been obvious over the prior art (*Id.* at 1531).

The Board of Patent Appeals and Interferences applied a similar line of reasoning in *Ex parte Tanksley and Bernatzky* (37 USPQ2d 1382 (BPAI 1994)). The appellants sought to patent a cDNA library for distinguishing between tomato varieties, comprising at least 2 marker clones from a list of 17 clones specified in the claims. Prior art cited by the Examiner related to other tomato cDNA libraries that had been developed during the course of studies by different groups of investigators. The appellants provided a 37 CFR § 1.132 Declaration, establishing that the likelihood of two independently derived libraries containing identical clones was *so low as to be unworthy of serious consideration*. On this basis, the Board decided that the claimed invention was not obvious over the prior art, regardless of whether the prior art was enabling for what it disclosed. Accordingly, the prior art rejections were reversed. (A new ground of rejection was entered on a different basis.) This opinion is binding precedent of the Board (*Id.* at 1382).

The improbability of reproducing the claimed invention is not overcome by a detailed prior description of the substance that is claimed. In *In re LeGrice,* the court recognized that the

art did not allow rose-breeders to direct cross-breading towards an exact phenotype. No *post hoc* selection criteria can compensate where the number of possible species to select from renders the task overwhelmingly improbable.

The court reversed the decision of the Board of Appeals with the following conclusion:

> The mere description of the plant is not necessarily an "enabling" disclosure. Such descriptions, just as in the case of other types of inventions, in order to bar the issuance of a patent, must be capable, when taken in conjunction with the knowledge of those skilled in the art to which they pertain, of placing the invention in the possession of the public.
>
> The descriptions of the new roses in the instant publications, are incapable of placing these roses in the public domain by their descriptions when interpreted in the light of the knowledge now possessed by plant breeders. The roses disclosed in the appealed applications are not, therefore, "described in a printed publication" within the meaning of 35 USC 102(b).
>
> – *In re LeGrice* at 378; footnotes omitted.

2. Uniqueness of antibody sequences as a feature of the generation of antibody diversity

Just as it is improbable to reproduce a particular rose species or a particular tomato library from a genetic parent, it is improbable to reproduce a particular antibody molecule by immunizing a second animal with the same antigen.

Antibodies are different from other mammalian proteins, in that affinity maturation results in a considerable reengineering of the sequences intrinsic to the molecule. The amino acid sequences of both the heavy and light chain variable region are affected. This mechanism results in a wide diversity of amino acid sequences for antibodies with similar specificities.

The possibility of two antibody-producing cell lines from different animals comprising complete identical variable region genes *before mutation* is small; the possibility of two such cell lines comprising *identically mutated* variable region genes is so vanishingly small as to be essentially nil.

This section outlines what is known in the art about the generation of antibody diversity (for a classic review, see Tonegawa (1983), Nature 302:575.) Immunoglobulin heavy chain genes arise in the B cell lineage from rearrangement of about 25-200 variable region genes, about 10 D regions, and about 5 J regions, with the order of 100 splice variants being possible for each V-D-J combination. Except for the lack of a D region, formation of a complete light chain gene is nearly as complex. Different heavy chains may associate with different light chains. The total number of combinatorial possibilities is therefore well over 10^8.

Only a proportion of these combinatorial possibilities yield viable antibody molecules with a particular specificity. However, another level of diversification is introduced following gene rearrangement. Antibody-producing B cells which are specific for an immunogen undergo *further* diversification by deliberate *somatic mutation* of the rearranged heavy and light chain variable region genes (reviewed, e.g., in Kochs et al. (1989), Ann. Rev. Immunol. 7:537; Berek et al. (1988), Immunol. Rev. 105:1). Mutation is believed to occur at a rate of about 10^{-5} per base pair per generation at the pre-B cell stage. It increases to nearly 10^{-3} per base pair per generation (almost one mutation per cell per generation) between 7 and 14 days following antigen exposure, when selected clones begin to enter the memory compartment. Some of the results of this mutation process are the emergence of clones with modified specificity, higher affinity, faster forward rate constants, and combinations thereof. However, mutations may occur anywhere within the entire length of the heavy and light chain variable region, including regions well outside the antigen-binding site. At the DNA level, even 5' and 3' untranslated regions of the DNA may be mutated.

In addition, it is clear that there are a vast number of possible antibody sequences that bind any particular antigen. When two different animals are immunized with the same antigen, they may each produce antibodies against it, but the antibody molecules obtained represent different solutions to the requirements of an antigen binding site. Accordingly, different antibody-producing cell lines cloned from a response against the same antigen will have substantially different variable region sequences.

This is illustrated in various experiments in which panels of monoclonal antibodies have been produced using haptens as the immunizing antigen. Haptens are small chemical groups, comprising only a single epitope. Yet, the antibodies raised against them have widely diverse amino acid sequences. Illustrative studies by Nahmias et al., Stenzel-Poore et al., Blier et al. and Leahy et al. are outlined in *Appendix A* to this paper.

These experiments illustrate that gene selection, gene splicing, and somatic mutation all contribute to widely diverse sequences that may be produced against any particular antigen. Somatic mutations accumulate as B cells pass through the memory compartment. Amino acid substitutions may occur at nearly any position in the light and heavy chain variable regions, as long as the replacement does not impair specificity. Antibody produced by a clone that has gone through the memory compartment comprises a number of such substitutions. The number of possible sequences for an antibody of any particular specificity is immense.

The steps of gene selection, gene splicing, and somatic mutation all occur independently of antigen. What creates the specificity of the antibody response is the preferential *selection* of clones of the desired specificity by antigen by interacting with antibody-producing cells *already expressing the assembled antibody at the cell surface.* Accordingly, the clones selected by antigen incorporate two types of changes: a) *those that enhance binding to antigen*; and b) *those that have a neutral effect on antigen binding.*

For changes that enhance binding to antigen, there are a large number of possible alternatives, both as to the amino acid used, and their location within the variable region. It is unusual that a particular amino acid mutation is absolutely required without the possibility of an alternative in order to bind directly to antigen. Mutations that enhance binding are generally found elsewhere within the variable region, and act to stabilize the preferred antigen-binding pocket (reviewed recently in Patten et al.; see also Strong et al.). Presumably, all substitution or combination of substitutions that generate comparable degrees of stability to the antigen binding pocket will serve the purpose, and would therefore be equally selectable by antigen.

Changes that have a neutral effect on antigen binding will necessarily occur during the somatic mutation process, which is known to occur throughout the variable region gene (and into neighboring untranslated regions). Many of the mutations occurring outside the antigen-binding regions, or outside the complementarity-determining regions (CDRs), probably come within this category. Strong et al. found that only 6 of 16 somatic mutations in a monoclonal antibody contributed to the enhancement of affinity to the antigen, anti-*p*-azophenylarsonate. Blier et al. provide experimental evidence that changes non-deleterious to binding of the antigen NP accumulate during affinity maturation. They found that even after gene rearrangement and an initial round of somatic mutation, various sub-lines from a common ancestor appeared to accumulate additional mutations while retaining similar antigen-binding properties. Changes unrelated to antigen binding are especially hard to regenerate, since they are neither antigen-driven nor antigen-selected.

The hapten experiments outlined in *Appendix A* provide empirical demonstrations of how different antibodies with the same specificity from the same strain of mice may be. For example, the twelve anti-DNP spin label antibodies of Leahy et al. (*Appendix A*, Figs. 1 & 2) showed an average variability of about 4 alternative amino acids at 83% of the positions in the amino acid sequence.

3. Uniqueness of the 1A7 sequence

An analysis of 1A7 demonstrates that it has the characteristics of a mature antibody that make it virtually impossible to reproduce.

The 1A7 monoclonal antibody was developed by immunizing and selecting with the murine mAb 14G2a (specification: page 13, lines 18-20; page 14, lines 4-6). Four immunizations were required to obtain a response (page 13, lines 20-22), as opposed to the usual requirement of two immunizations for a mature anti-hapten response. Therefore, the clone emerging with anti-14G2a specificity had been through the memory compartment and subjected

to a period of somatic mutation at least once, and possibly three times. The number of possible sequences for an anti-idiotype antibody with specificity for 14G2a is expected *a priori* to be at least as large as described in the previous section for an anti-hapten antibody.

The extensive role of somatic mutation in generating the 1A7 sequence is confirmed by the sequence data. The polynucleotide sequences and amino acid translations of the 1A7 heavy and light chain variable regions have been obtained by Dr. Sunil Chatterjee, University of Kentucky. The sequence data and an analysis thereof is outlined in the 37 CFR § 1.132 Declaration by Dr. Sunil Chatterjee, which is filed herewith.

As illustrated in *Exhibit B* of the Declaration, the 1A7 amino acid sequences were compared with all known sequences in databases sourced by the National Center for Biotechnology Information using the BLAST alignment algorithm. The comparison demonstrates that in addition to features generated by gene selection and rearrangement, there are about 16 point differences between 1A7 and the amino acid sequences encoded in the germline genes from which it was derived.

The 1A7 *light* chain differs from the closest amino acid sequences in the prior art in at least two positions within the variable region. These differences lie in the second complementarity determining region. The 1A7 *heavy* chain differs from the 50 closest amino acid sequences by a minimum of about 14 deletions or insertions, and usually by at least 22 such changes. The substitutions occur between residues 1-97, corresponding to the V_H gene, and after residue 97, corresponding to the D and J_H genes. The insertions and deletions are splice variants about the VDJ junction. Thus, *the 1A7 heavy chain was generated by a rare splice event, followed by extensive somatic mutation.*

The last page of *Exhibit B* of the Sunil Chatterjee Declaration provides a determination of the prototype sequence from which 1A7 was derived. The prototype sequence is the possible rearranged VJ light chain and VDJ heavy chain germ line sequences that were subsequently mutated to give the mature sequence found in 1A7. The 1A7 amino acid sequences differ in 2 positions from the prototype light chain variable region, and at least 14 positions from the heavy

chain variable region. Accordingly, it is likely that about 16 mutation events occurred in the generation of 1A7, of which 9 are outside the CDRs.

Appendix B of this paper provides a calculation for the number of possible antibody molecules that is as extensively mutated as 1A7 and capable of binding the same antigen. *Even with conservative assumptions, the number of molecules is of the order of* 10^{30}. Gene selection, splicing, and somatic mutation all contribute to this range. A major contributing factor is the wide variation in the number of locations that possible mutations (including those irrelevant to antigen binding) may occur within the sequence.

The accompanying 37 CFR § 1.132 Declaration by Malaya Bhattacharya-Chatterjee indicates that only 1 out of 1024 wells cultured from 4 immunized mice produced antibody of the desired specificity. Because so few specific cells can be identified, fused, and expanded from each immunized mouse, *it would take at least about* 10^{27} *mice to obtain a hybridoma line producing such a rare antibody molecule.*

Applicants' argument does not depend on the exactness of the probability calculation. It is applicants' position that any antibody that would require a very large number of mice to reproduce, combined with the extensive fusion, culturing, screening, cloning and competition-testing that is subsequently required, is beyond the scope of reproducibility in any practical sense.

In summary, in view of the extensive mutation in 1A7, it is in all practical terms impossible for anyone to obtain 1A7 by immunizing a second animal, even using the exact protocol used to obtain 1A7.

4. Lack of availability of 1A7 cell line, antibody, or sequence data

Because of the uniqueness of the 1A7 antibody and the virtual impossibility of regenerating it in a second animal, the invention may only be practiced:

1. By obtaining the antibody (or the antibody encoding gene) from the 1A7 hybridoma line; or
2. By synthetically producing an antibody with identical amino acid sequences, based on the 1A7 sequence data.

Filed herewith is a 37 CFR § 1.132 Declaration by Malaya Bhattacharya-Chatterjee, establishing that the claimed invention has not been provided to the public. The cell line and antibody have been used only for developmental and experimental work under control of the inventors. The sequence data has been kept confidential.

Since the 1A7 antibody, the 1A7 hybridoma, and the sequence data were and are not available to the public, the invention cannot be said to be in the possession of the public.

5. Application of the legal standard to the present application

Because of the uniqueness and unavailability of 1A7, the present case is the antibody equivalent of the cases discussed *supra* that set the legal standard for a § 102 reference.

In particular, the abstract by Bhattacharya-Chatterjee et al. cited against the claimed invention is analogous to the catalog disclosure that the examiner cited as a 102(b) reference in *In re LeGrice*. Bhattacharya-Chatterjee provide the genetic origin of the 1A7 hybridoma clone, in the form of the immune repertory of the BALB/c mouse strain. This is analogous to the genetic origin of the "Charming Maid" rose, disclosed in the catalog cited in *In re LeGrice* as the parentage. Bhattacharya-Chatterjee provide some desirable characteristic of the 1A7 antibody; namely, that it binds to mouse anti-GD2, either mAb 14G2a or Ab3. This is analogous to the several desirable characteristics of the rose variety that are provided in the description and representation in the catalog.

The analogies between the two cases lead to the same conclusion. The genetic origin and desirable characteristic of 1A7 disclosed in Bhattacharya-Chatterjee are no more useful in predicting or reproducing the genetic composition of the 1A7 encoding genes than the catalog

disclosure was in predicting or reproducing the genetic composition of "Charming Maid". The public is no more able to reproduce 1A7 using the description in the abstract than it was able to reproduce "Charming Maid" using the description in the catalog.

Accordingly, the abstract of Bhattacharya-Chatterjee does not enable the claimed invention, and is inadequate as a reference for purposes of rejection under 35 USC § 102(b).

Case law underlines the public policy objective to place inventions into the hands of the public through the patent process. The subject application explicitly claims the 1A7 antibody. The claimed invention is not presently in the hands of the public, because the art of record does not provide a source of the 1A7 monoclonal antibody or its sequence. The public policy objective will be met by issuance of a patent for the claimed invention.

Accordingly, applicants respectfully request that this rejection be withdrawn.

<u>35 USC § 103 rejection over Saleh et al.</u>

Claims 1-3 were rejected under § 102(b) or alternatively under § 103 over Saleh et al. Claim 1 has been amended, and claims 2 and 3 have been canceled. Claims 10-12 pertain to the 1A7 antibody, the 1A7 producing cell line, and antibody preparations therefrom. Applicants gratefully acknowledge withdrawal of the § 102 argument as a result of the interview of January 25, 1996 (Paper No. 9).

Saleh et al. disclose a human monoclonal anti-idiotype that was induced by 14G2a and is capable, under limited circumstances, of inducing an anti-GD2 response. Applicants respectfully traverse the § 103 rejection, and ask that it be reconsidered and withdrawn.

In traversing the rejection of these claims under 35 USC § 103, applicants reiterate the submissions made *supra* regarding § 102(b) rejections over Bhattacharya-Chatterjee et al. There is a similar enablement requirement for 35 USC § 103 references to place the invention into the hands of the public. See, e.g., *Beckman Instruments, Inc. v. LKB Produckter AB*, 13 USPQ2d 1301 (Fed. Cir. 1989). Saleh et al. does not place the 1A7 monoclonal antibody into the hands of

the public, because it does not provide the public with the 1A7 antibody or the hybridoma cell line, nor does it teach or suggest the amino acid sequence that is unique to the 1A7 monoclonal antibody.

Furthermore, the teachings of Saleh et al. do not provide the practitioner with either the motivation or a reasonable expectation of success to produce an antibody with the exact characteristics of 1A7. As anyone of skill in the art knows, an immunizing antigen is much more immunogenic in a different species than the species from which it is originally derived. The immunizing antibody in the present invention and in Saleh et al. was the monoclonal antibody 14G2a. This is a *mouse* antibody. Saleh et al. teach only that it is immunogenic and can be used to generate an anti-idiotype in *humans*. Those in the art would reasonably doubt that 14G2a is be immunogenic in mice, since fewer epitopes within the 14G2a idiotype will be viewed as foreign in mice. It is even less predictable from Saleh et al. that a monoclonal antibody obtained in a species homologous to the immunogen would be capable of inducing a GD2 response.

The natural impediments to generating a mouse-anti-mouse response was overcome in generating 1A7, *inter alia,* by: a) conjugating 14G2a to KLH (specification, page 11 line 20); adopting an unusual immunization schedule in which mice were immunized biweekly over the course of 2 months (page 13 lines 20-23); and c) assaying sera regularly and not harvesting the cells for fusion before the desired activity was obtained (page 13 lines 23-28). These procedures are not described in Saleh et al.

Applicants respectfully request that this rejection be withdrawn.

35 USC §§ 103 rejection over Cheung et al. and Mujoo et al.

Claims 1-4 and 7-9 were rejected under 35 USC § 103 over Cheung et al. in light of Mujoo et al. Claims 1, 4, and 7-9 have been amended, and claims 2 and 3 have been canceled. New claims 10-12 pertain to the 1A7 antibody, the 1A7 producing cell line, and antibody

preparations therefrom. New claims 13-26 pertain to similar subject material as pending claims 4 and 7-9.

Cheung et al. teach the preparation of an anti-idiotype capable of inducing anti-GD2. Mujoo et al. teach the 14G2a antibody. Applicants respectfully traverse the rejections, and ask that they be reconsidered and withdrawn.

In traversing the rejection, applicants rely in the first instance on submissions made *supra* regarding § 102(b) rejections over Bhattacharya-Chatterjee et al. Cheung et al. and Mujoo et al., either alone or in combination, do not place the 1A7 monoclonal antibody into the hands of the public, because they do not provide the public with the 1A7 hybridoma cell line, nor do they teach or suggest the particular characteristics of 1A7, including the amino acid sequences that are unique to 1A7. They also do not teach or suggest the ability of 1A7 in particular to actively induce an anti-GD2 response.

In addition, applicants submit: a) there is no motivation to combine the references; b) based on the references alone, there is no reasonable expectation of success with regards to making an anti-idiotype with the desirable properties of 1A7.

First, motivation to combine the references is lacking. Mujoo et al. teach the Ab1 (namely, 14G2a) that was used to generate 1A7, along with several *other* anti-GD2. However, there is no suggestion that any of the anti-GD2, and 14G2a in particular, would be suitable to induce an anti-idiotype, especially one that has the vaccine potential of 1A7. Conversely, Cheung et al. does not teach or suggest that the 3F8 antibody they used to generate their anti-idiotype can be substituted by any other Ab1, and in particular 14G2a. Considering the myriad of Ab1 there are available against melanoma associated antigens (GT1b, GD3, GM1, GM2, and GM3, and others outlined in the Background section of the specification), the ordinary practitioner is not directed to combine a particular antibody developed by Mujoo et al. as an Ab1 in the protocol described by Cheung et al.

Second, the ordinary practitioner would not have a reasonable expectation of obtaining an anti-idiotype with the same useful properties as 1A7, based on the cited references. The antibody

of Cheung et al. is considerably less effective than 1A7 in its qualities as a vaccine component. They state: "Although [their] rat anti-idiotypic antibodies could induce circulating antibodies against ganglioside GD2 in mice, the titers were generally low after primary immunization. Even though the titers were elevated after boosting, most of the antibodies detected were of the IgM class ... the fine specificity of these antibodies could not be determined ...". In order to obtain substantial quantities of Ab3, Cheung et al. had to immunize *with the intact hybridoma cells,* a procedure inappropriate for most forms of clinical treatment. In contrast, the 1A7 antibody readily induces Ab3 in mice, rabbits, and primates (specification; page 15, line 15 to page 16, line 13). The Ab3 is produced in sufficient quantity and with sufficient affinity to be isolated by affinity chromatography under conditions that suggest it is a mature IgG antibody.

Applicants respectfully request that this rejection be withdrawn.

SUMMARY AND CONCLUSION

Applicant respectfully submits that none of the art cited against the claimed invention reaches the standard required for rejection under 35 USC §§ 102 and 103. *Inter alia,* the references fail to place in the hands of the public the means to make or use monoclonal antibody 1A7, or compositions or diagnostic kits containing 1A7. The instant application meets the enablement requirements of 35 USC § 112 ¶ 1.

Accordingly, applicants request that all objections and rejections be reconsidered and withdrawn. Applicants further submit that newly added claims 10-26 are patentable over inventions previously in the possession of the public. Applicants respectfully request allowance of all pending claims currently under examination.

Respectfully submitted,
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